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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/060,697
Filing Date: January 30, 2002
Appellant(s): PETERSEN, DONALD W.

Christopher M. Humphrey
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 11, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences that will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the issues in the brief is substantially correct. *The Examiner's Answer contains a new grounds of rejection. See Section 12 infra.*

(7) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Prior Art of Record

4,484,601	O'Leary et al.	1-1996
5,385,887	Yim et al.	1-1995
WO9840113	Wironen	9-1998

GB999,487 Baillie et al. 7-1965

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 16-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of O'Leary et al. (5,484,601), Yim et al. and WO 9840113 taken as a whole.

Claim 16 recites a bone graft substitute composition comprising calcium sulfate, a mixing solution, a plasticizing substance, cancellous bone and demineralized bone matrix. Dependent claims specify the amounts of the components and recite specific substances that are used for the calcium sulfate component, the mixing solution component and the plasticizing substance component. The specification discloses that the object of the invention is to create a bone graft substitute composition that has "extended set time and sufficient robustness to withstand fluid impact with minimal erosion for expanded clinical application."

O'Leary et al. disclose a flowable demineralized bone matrix composition for use in bone repair. O'Leary et al. state at col. 1, lines 36-43 that "[I]t is a particular object of the invention to provide a composition of liquid or pastelike consistency comprising demineralized osteogenic bone powder and a biocompatible liquid synthetic organic material as a carrier for the bone powder with or without such optional ingredients as thixotropic agents, medicaments, and the like, and to apply the composition at a bone defect site to induce new bone ingrowth at the site." At col. 3, lines 14-20, the patent states "[t]o provide the demineralized allogeneic bone powder composition of this

invention, the demineralized bone powder with or without any of the foregoing optional components mentioned above absorbed therein is combined with a biocompatible liquid synthetic organic material which functions as a carrier or suspension agent for the bone powder." The patent further defines the terms "liquid" and "flowable" as "intended to include (1) organic materials which in the pure or highly concentrated state and at ambient temperature, e.g., 15-40° C. are flowable liquids and (2) organic materials which in the pure or concentrated state and at ambient temperature are normally solid but dissolved in a suitable solvent, e.g., water or a biocompatible organic solvent such as ethanol, can be provided in liquid form. Functionally, the liquid component of the composition serves to provide a flowable material of widely varying consistency. The term "flowable" as used herein applies to compositions whose consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like putty, to those which are runny. Specific forms of flowable bone powder compositions include cakes, pastes, creams and fillers." O'Leary et al. disclose at col. 3, line 56 to col. 4, line 6 that "[w]here, in a particular bone powder composition, the bone powder has a tendency to quickly or prematurely separate from the carrier or to otherwise settle out from the composition such that application of a fairly homogeneous composition is rendered difficult or inconvenient, it can be advantageous to include within the composition a substance whose thixotropic characteristics prevent or reduce this tendency. Thus, e.g., where the carrier component is glycerol and separation of bone powder occurs to an excessive extent where a particular application is concerned, a thickener such as a

solution of polyvinyl alcohol, polyvinylpyrrolidone, cellulosic ester such as hydroxypropyl methylcellulose, carboxy methylcellulose, pectin, food-grade texturizing agent, gelatin, dextran, collagen, starch, hydrolyzed polyacrylonitrile, hydrolyzed polyacrylamide, polyelectrolyte such as polyacrylic acid salt, etc., can be combined with the carrier in an amount sufficient to significantly improve the suspension-keeping characteristics of the composition. Finally, O'Leary et al. disclose at col. 2, line 53 to col. 3, line 13, that "[a]ny of a variety of substances can be introduced into the bone particles" and includes a non-limiting list which includes inorganic elements, parenchymal cells, growth factors, bone morphogenic proteins, and mesenchymal elements.

Therefore, O'Leary et al. provides the motivation to produce a bone graft substitute composition containing a mixing solution, a plasticizing substance consistent with those described in the specification and demineralized bone matrix. Further limitations of the claims are also disclosed by the patent. For example, the claims require the presence of 10-100 parts by weight of demineralized bone matrix. O'Leary et al. teach at col. 4, lines 18-22 that "[t]he amount of bone powder which can be incorporated into the composition of this invention can vary widely with amounts of from about 5 to about 80 weight percent, and preferably from about 20 to about 60 weight percent, being entirely suitable in most cases." That which the specification defines as a "plasticizing substance" (cellulosic esters such as hydroxypropyl methylcellulose and carboxy methylcellulose) is identified as included in the composition of O'Leary as a thixotropic agent.

While there is no explicit disclosure of the presence of calcium sulfate or cancellous bone, it is noted that the O'Leary patent clearly teaches that "any variety of substances" can be introduced to the composition include "inorganic elements".

Yim et al. discloses a composition for delivery of osteogenic proteins for the purpose of promoting the growth of bone at the site of the delivery of the proteins. The patent states that "the subject invention involves pharmaceutical formulations designed to sequester osteogenic protein in situ for a time sufficient to allow the protein to induce cartilage and/or bone formation." Yim et al. teach that "[o]steogenic proteins are those proteins capable of inducing, or assisting in the induction of, cartilage and/or bone formation. Many such osteogenic proteins have in recent years been isolated and characterized, and some have been produced by recombinant methods. For example, so-called bone morphogenic proteins (BMP) have been isolated from demineralized bone tissue." Yim et al. further teach that "[I]n U.S. Pat. No. 5,171,579, it is disclosed that osteogenic proteins can be sequestered at a site where bone inducing activity is desired using autogenous blood, without using antifibrinolytic agents, provided that a porous particulate polymer matrix is incorporated into the formulation. To reduce the preparation time and improve the above formulation's handling characteristics, [Patentees] have surprisingly found that it is desirable to add a calcium sulfate hemihydrate-containing substance (CSHS). The CSHS is preferably either pure calcium sulfate hemihydrate, also known as Plaster of Paris (POP), or a mixture of POP and hydroxyapatite (POP:HA). Adding a CSHS

reduces setup time and provides improved moldability and consistency of the resulting formulation.

Yim et al. state that the osteogenic proteins can be utilized in the form of a pharmaceutically acceptable solution and cites sodium chloride as an appropriate solubilizing agent, as well as multiple different aqueous solutions of amino acids and other acids. See col. 3, line 53. Further, at col. 4, lines 32-33, the osteogenic protein formulations may be lyophilized and reconstituted with water prior to use. Yim et al. also include a "porous particulate polymer matrix component" that acts as an "in situ scaffolding for the osteogenic protein, while having biodegradable properties allowing for replacement by new bone growth" as well as a "protein-sequestering material". This material is used to "hold" the osteogenic proteins at the site for a sufficient time to allow them to have a bone growth promoting effect. This may be a blood clot from autogenous blood. Yim et al. states that "[i]n the absence of such blood clot, osteogenic protein desorbs from the [particulate polymer matrix] particles in situ at a rate such that the osteoinducing effect of the protein is not clinically significant." Suitable "protein-sequestering agents" are disclosed at col. 7, lines 25-34, as cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose." The cellulosic protein sequestering agent is preferably present in a concentration of about 2 to about 10% (w/v). Determination of the quantity of the calcium sulfate hemihydrate is disclosed as being well within the skill of the practitioner and is determined to be that quantity which

provides the best handling properties both immediately after and 1 to 2 hours after preparation will be optimal. The formulations of the disclosure of Yim et al. provide "malleable implants that allow therapeutically effective amounts of osteoinductive protein to be delivered to an injury site where cartilage and/or bone formation is desired. Such an implant may be used as a substitute for autologous bone graft in fresh and non-union fractures, spinal fusions, and bone defect repair in the orthopaedic field; in cranio/maxillofacial reconstructions; for prosthesis integration, especially as a surface coating to improve fixation of prosthetic implants such as hydroxylapatite coated prostheses; in osteomyelitis for bone regeneration; and in the dental field for augmentation of the alveolar ridge and periodontal defects and tooth extraction sockets. When used to treat osteomyelitis or for bone repair with minimal infection, the osteogenic protein may be used in combination with porous microparticles and antibiotics, with the addition of protein sequestering agents such as alginate, cellulosics, especially carboxymethylcellulose, diluted using aqueous glycerol." The patent further states that "[t]he lower viscosity formulations may also be used as a percutaneous injection to accelerate healing of closed fractures. In certain of these uses, the compositions of the subject invention may be used in combination with various bone cements, including erodible bone cements such as poly(propylene-co-fumarate) and certain hydroxyapatite cements. Also, certain of these uses will utilize bioerodible hardware such as erodible plates, screws, etc. As alluded to above, the dosage regimen will be determined by the clinical indication being addressed, as well as by various patient variables (e.g. weight, age, sex) and clinical presentation (e.g.

extent of injury, site of injury, etc.). In general, the dosage of osteogenic protein will be in the range of from about 10 to 1000 μg, preferably from about 10 to 100 μg."

Therefore, Yim et al. provides the disclosure of a bone graft substitute composition, similar to O'Leary et al., which contains calcium sulfate, a mixing solution, and a plasticizing substance and which has improved moldability and consistency. The bone morphogenic proteins of the Yim reference, while not identical in composition to demineralized bone matrix of the claims, serves the same purpose, i.e. the delivery of bone growth promoting proteins to a site of bone injury. As noted previously, bone morphogenic proteins are present in demineralized bone matrix, and are obtained via extraction of demineralized bone matrix. The patent also discloses further limitations of the claims. For example, the claims require specific mixing solutions. Yim et al. discloses, in a non-limiting list, both water and sodium chloride as a solvent present in the composition for the osteogenic proteins. Since calcium sulfate hemihydrate (plaster of paris) requires an aqueous solution to activate it and allow it to harden, one of ordinary skill in the art would be aware such a solution would be necessary and the selection of either sterile water or saline or other buffers is deemed conventional and well within the skill of the practitioner. To that end, it is noted that the patent to Yim et al. clearly acknowledges that a composition containing calcium sulfate hemihydrate must be kept dry until the time of its use since the addition of an aqueous solution causes the activation of the calcium sulfate hemihydrate and results in ultimate hardening of the calcium sulfate hemihydrate (such as seen with the use of plaster of paris). Yim et al. state at col. 8 that "[t]he osteogenic protein and porous particles of

the formulations may be provided to the clinic as a single vial formulation, either as a solution or in lyophilized form, or the formulation may be provided as a multicomponent kit wherein, e.g. the osteogenic protein is provided in one vial and the porous particles and calcium sulfate hemihydrate-containing substance each are provided in separate vials." Further, Yim et al. discloses the mixing of the osteogenic proteins in solution with the calcium sulfate hemihydrate. The aqueous solvent of the osteogenic proteins, such as water or sodium chloride, would be expected to activate the calcium sulfate hemihydrate. When including the calcium sulfate hemihydrate component into the composition of O'Leary et al., one of ordinary skill in the art would be aware and motivated to provide an aqueous activating mixing solution since the bone morphogenic proteins are contained within the dry demineralized bone matrix .

The claims also require the presence of approximately 1 to 40 parts of the plasticizing substance by weight. Yim et al. teaches at col. 7, lines 40-45, that the cellulosic protein sequestering agent is preferably present in 2-10% (w/v). The claims define the specific cellulose derivatives. Plasticizing substances such as recited in the claims are identified as included in the composition of Yim et al. as a protein sequestering agent.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of O'Leary et al. with components of the composition of Yim et al. Both O'Leary et al. and Yim et al. have the same object in creating a malleable, workable bone growth promoting composition. One of ordinary skill in the art when reviewing the disclosure of Yim would have been

motivated to include a calcium sulfate component into the composition of O'Leary et al. with the expected benefit disclosed by Yim et al., i.e. that a calcium sulfate component would add improved handling, moldability and consistency to the formulation of O'Leary as well as reducing the set up time. The compositions of Yim and O'Leary are so sufficiently similar that one of ordinary skill in the art at the time the invention was made would be aware of the properties of the calcium sulfate hemihydrate would not impair or otherwise negatively affect the components of the O'Leary composition. Both compositions contain components that provide either directly or indirectly osteogenic proteins, and both compositions contain a cellulosic material that is being used for the same purpose, i.e. to impart viscosity and suspension properties to the respective compositions. The general amounts of both the demineralized bone matrix and the cellulose material are taught by the references. The optimization of the amount of calcium sulfate and mixing solution to be further included is deemed well within the skill of the practitioner at the time the invention was made as it is clear that the amount of calcium sulfate is directly related to desired rate of set up of the composition, i.e. the more calcium sulfate used, the faster the composition will set up and harden. Further, it is clear that the amount of mixing solution is inversely related to the desired set up time and directly proportional to the ultimate consistency of the composition, i.e. the more mixing solution used, the more dilute the calcium sulfate and the slower the set up time but the more liquid the composition will become.

Finally, the claims recite the further inclusion of cancellous bone. Both patents teach that other conventional components included in bone growth promoting

compositions may be included in the disclosed compositions. The disclosure of WO 9840113 is also drawn to a bone paste for the repair of bone defects. The disclosed paste contains demineralized bone matrix, an inorganic component such as ceramics hydroxyapaptite and calcined bone, or bone morphogenic proteins or other growth factors and mixtures thereof. Other ingredients that may be present in the paste include wetting agents and carboxymethyl cellulose (see pages 5-6). At page 13, the reference states that the composition "may act as a carrier for cortical, cancellous or cortical and cancellous bone chips. Such compositions are useful for filling larger bone voids. In addition, when these bone chips are not demineralized, they provide an added spectrum of biological properties not exhibited by the gelatin alone or the gelatin plus the osteogenic components (i-iv)."

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include cancellous bone chips into the composition of O'Leary et al. for the benefit described in the disclosure of WO 9840113, i.e. they fill larger bone voids and provide an added spectrum of biological properties to the composition.

It is clear that the components as claimed are all well known to be included in bone graft compositions. It is clear that there is a benefit to the formulation of the composition as a moldable composition. The prior art clearly indicates that plasticizing substances such as are claimed are known to be used in prior art moldable bone graft compositions expressly for the purpose of improving the moldability of the composition. It is also clear that demineralized bone matrix is conventionally included in a moldable

bone graft composition for the purpose of acting as an osteoinductive agent by delivering bone morphogenic proteins to the area of the desired bone graft. It is also clear that the addition of calcium sulfate hemihydrate, an inorganic compound that becomes moldable when wetted and then ultimately hardens, is both well known and imparts another beneficial property to moldable bone grafts such that the grafts are moldable when inserted into the desired area but harden in that area such that they are not washed away by body fluids nor expressed or moved by body motion. Finally, it is clear that it is conventional to include cancellous bone chips into moldable bone graft compositions for the benefit of both osteo-induction and as a large bone void filler. Applicants are claiming conventional bone graft composition ingredients combined in a conventional manner and in known amounts. Further, the state of the art of these components are so well known that optimization of amounts for the purpose of changing the both the flowable and "set-up time" properties of the composition are deemed well within the skill of the practitioner.

Appellants are advised that this Examiner's Answer contains a new grounds of rejection and are directed to Section 11 of the Answer.

(10) Response to Argument

Appellants argue that there is no motivation to combine the references; however, Appellants' arguments are made against each the reference individually. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Specifically, Appellants assert that there is no motivation to combine the calcium sulfate hemihydrate with the composition of O'Leary. Further, Appellants appear to be asserting that O'Leary teaches away from the combination by stating that

> "there is nothing in O'Leary to indicate that a composition that hardens or sets over time is envisioned. In fact, the reference suggests otherwise by describing the term "flowable" as including compositions with consistencies ranging from those that are "shape sustaining but readily deformable . . . to those which are runny" (column 3, lines 30-34). Further, we note that O'Leary suggests the use of a thickener if settling of the bone powder within the organic liquid is a problem. (column 3, lines 56-63). This also suggests that the composition is intended to maintain a liquid, flowable state for an extended period of time. Obviously, if the composition is intended to set into a hardened mass within a short period of time, settling would not be an issue.

Appellants' arguments are drawn only to the O'Leary reference and fail to address the rejection made over the references as a whole. The theme of Appellants' arguments about the patent to O'Leary revolve around Appellants' use of the terms "extended period of time" and "short period of time" as a requirement of the composition of O'Leary; however, these terms do not appear in the patent. In absence of these terms in the patent to characterize the object of the invention of O'Leary and since all bone graft compositions of the prior art are desired to be maintained in place to stimulate replacement by mineralized (and therefore hardened) bone tissue, Appellants' arguments are simply not germane to the rejection of record. See particularly, col. 1, lines 40-43 where the object of the invention is "to apply the composition at a bone defect site to induce new bone ingrowth at the site." New bone growth is not immediate and requires time; for example, bone growth to repair fractures takes up to three months for complete bone replacement in the area of the fracture. As a result, one of ordinary

skill in the art would interpret the term "flowable" as used by O'Leary to describe the condition of the composition for the purpose of handling of the composition during application to the bone defect. It would not be interpreted as a condition that is required to be maintained throughout the time period that the composition spends in situ at the bone defect.

Appellants further argue that

> "we note that O'Leary suggests the use of a thickener if settling of the bone powder within the organic liquid is a problem. (column 3, lines 56-63). This also suggests that the composition is intended to maintain a liquid, flowable state for an extended period of time. Obviously, if the composition is intended to set into a hardened mass within a short period of time, settling would not be an issue."

Any evidence of record does not support these assertions. Appellants are first reminded that O'Leary is using bone powder of an average particle size from about 0.1 to 1.2 cm. Demineralized bone is composed of the osteoid components of bone that are large proteins such as collagen and bone morphogenic proteins. Bone particles of this composition and size cannot and will not dissolve in the disclosed carriers. Settling relates to the homogeneity of the bone powder distribution in a carrier. Therefore, only bone powder suspensions can be formed and O'Leary is explicit that homogeneity and settling are important issues. Appellants are further reminded that the rejection maintained that one of ordinary skill in the art would be motivated to add the calcium sulfate hemihydrate to the composition of O'Leary. Hydrated calcium sulfate hemihydrate does not harden instantaneously and O'Leary states that the bone powder has a tendency to "quickly" separate from the carrier. Clearly, this "quick" separation occurs even during preparation and before the application of the bone graft composition

to the bone defect and equally as clearly, the thickener is required regardless of any other components.

Therefore, Appellants' arguments that the "teachings of O'Leary are manifestly inconsistent with the well-known properties of calcium sulfate hemihydrate solutions" and that "the addition of calcium sulfate hemihydrate to the O'Leary composition would have been avoided by one of skill in the art since the resulting composition would not have been expected to maintain a flowable state for an extended period of time, which is clearly the aim of the reference" are not supported by the disclosure of O'Leary and therefore not persuasive.

Appellants assert that "[a]lthough Appellants have discovered that the clamed plasticizing substance can forestall the calcium sulfate hemihydrate hardening reaction, this effect is not appreciated in the prior art." This statement is not accurate; in a related application (09/915997), the examiner cited GB 999,487 as evidence that cellulose derivatives such as methyl sodium carboxymethyl cellulose are known as set retardants for calcium sulfate hemihydrate (plaster of paris). **Appellants are advised that this reference is not cited herein as being used in the rejection but merely to rebut a statement made in Appellants' brief.** Notwithstanding Appellants' inaccurate statement, there is, in actuality, no need to identify the set retardation effects of the "plasticizing substance" in any of the prior art references since the references, taken as a whole, provide the motivation to combine the calcium sulfate hemihydrate of Yim with the composition of O'Leary. Appellants assert that

> As a result, one of ordinary skill in the art without the benefit of Appellants' disclosure would view the combination of calcium sulfate hemihydrate with the

> O'Leary formulation as likely to negate the flowability requirement set forth in O'Leary. Thus, for this reason, one of ordinary skill in the art would not find the requisite motivation to combine the calcium sulfate hemihydrate of Yim with the O'Leary composition.

Appellants also appear to be suggesting that O'Leary must identify the problem in order to provide the motivation to solve it; however, there is no requirement in the patent law as to which specific piece of prior art provides the motivation to combine the references. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). So long as at least one of the prior art references provides the motivation, the requirements of the statute are met.

Further, Appellants also err in requiring that any prior art document must explicitly identify a problem to be solved in another specific formulation in order to provide motivation. Yim shows that bone repair compositions that do not contain CSHS will have improved moldability upon the inclusion of the CSHS and provides a reasonable expectation of success based upon the known properties of CSHS. This teaching is not negated simply because Yim does not identify all specific extant bone repair formulations that do not contain CSHS. Again, such a requirement is not consistent with existing patent law and would, in fact, be onerous.

Appellants further state that

> Even ignoring the clear suggestion in the art to avoid combining calcium sulfate hemihydrate with O'Leary as discussed above, the Examiner's reasoning for combining Yim with O'Leary is inconsistent with the teachings of the Yim reference. As explained in the after-final office action response, Yim describes

> the use of calcium sulfate to reduce the preparation time or "set up time" of a composition comprising osteogenic proteins, autogenous blood and a porous particulate polymer matrix material. (column 2, lines 51-65). Presumably, calcium sulfate is useful in this composition to reduce setup time because of the relatively long period of time it takes for autogenous blood to clot in the formulation. Appellants note that this teaching is directly contrary to the present invention since the stated goal in Yim is to reduce set up time, not increase it.

Appellants' arguments are not persuasive because they are using the term "set up time" inconsistently. Yim uses the term "set up time" to be synonymous with "preparation time" of the composition. This is taken to mean the time to mix all of the ingredients to form a composition that is ready to be applied to the bone defect. In the art of hydration of calcium sulfate hemihydrate, "set time" is the time that any given calcium sulfate hemihydrate composition to harden. See previously cited GB 999,487, col. 1. Since the time a composition takes to harden is directly dependent upon the amount of calcium sulfate hemihydrate, the amount of hydrating solution and the presence and amount of any set retardant in the composition, the "set" time is fixed for any given combination. Therefore, the "set time" of the composition of Yim occurs after the composition has been prepared and administered (defined by Yim as the "set up time"). These two times are only related insofar as it is clear that the composition must be administered after the "set up time" (i.e. after the composition is prepared) but cannot be administered after the "set time" (because the composition would be hardened at that time and could not be manipulated sufficiently to be placed into the desired defect).

Appellants state that "Yim does not provide a general suggestion that calcium sulfate provides such advantages in all bone graft compositions." Appellants again assert that the teaching of the Yim reference must be limited to a suggestion to combine

a calcium sulfate hemihydrate-containing substance (CSHS) with the formulation of U.S. Patent 5,171,579 that is a formulation of osteogenic proteins, a blood clot and a porous particulate polymer matrix. Appellants state

> The Examiner responded to this argument in the Advisory Action by noting that Yim describes the addition of calcium sulfate hemihydrate to other compositions as well, such as the suggestion at column 2, lines 27-31 to form a composition containing calcium sulfate hemihydrate and an osteogenic protein. Yet, the Examiner continues to rely on the improved handling/moldability teaching in Yim as the motivating factor for the alleged combination. The Yim reference does not teach that improved handling/ moldability will be realized in the other embodiment noted by the Examiner. The osteogenic protein/calcium sulfate hemihydrate embodiment is described more fully at column 8, lines 16-28, where the reference teaches that, in that embodiment, calcium sulfate hemihydrate provides a structural matrix function, an osteoconductive matrix and a protein sequestering function. There is no discussion of improved handling whatsoever.

Appellants' arguments are misplaced. Again, there is no requirement that there be any express statement of benefit for every formulation disclosed by Yim. Further, it remains unclear as to why Appellants believe that all formulations of Yim (which are taught to contain calcium sulfate hemihydrate) would not all have the benefit that Yim specifically relates to the addition of the calcium sulfate hemihydrate. A composition and its properties are not separable. Appellants have provided no objective evidence of record to support this conclusion.

Finally, with regard to the reference to Yim, Appellants argue that the Examiner's assertion in the Advisory Action that Yim teaches four of the five claimed ingredients of Appellants' composition is improper as the Examiner stated that, since demineralized bone matrix can contain bone morphogenic proteins (BMPs), Yim's description of the use of BMP'S encompasses demineralized bone matrix. This argument is also

unpersuasive. The Examiner used this analysis to point to the similarities between the composition of Yim and the composition of O'Leary. The Examiner did not "attempt to broaden the unambiguous teachings of Yim"; however, as evidenced by the Background of the Invention of O'Leary, it is clear that demineralized bone matrix is a way to deliver BMPs to bone defects and therefore, as combined with Yim would act as a suggestion to use demineralized bone matrix as an alternative to purified BMPs.

With regard to the Wironen reference, Appellants argue that there is no motivation to combine it with the references to Yim and O'Leary. Again, Appellants are improperly arguing the references individually rather than as they are applied, their teachings taken as a whole. Appellants appear to be arguing that the Wironen reference contrasts the gelatin carrier of Wironen with a commercial embodiment of O'Leary; however, the teaching of O'Leary is not limited to its preferred embodiments. Further, Wironen was not included to motivate the combination of the entire composition of Wironen with the entire compositions of Yim and O'Leary. Appellants assert that due to the "marked difference" between the composition of Wironen and the compositions of Yim and O'Leary, that this "marked difference" is sufficient to provide no motivation to combine the references. In fact, Appellants ignore the marked similarities between the composition of Wironen and those of Yim and O'Leary. The disclosure of Wironen is also drawn to a bone paste for the repair of bone defects. The disclosed paste contains demineralized bone matrix, an inorganic component such as hydroxyapaptite and calcined bone, or bone morphogenic proteins or other growth factors and mixtures thereof. Other ingredients that may be present in the paste include wetting agents and

carboxymethyl cellulose (see pages 5-6). As stated above, at page 13, the reference states that the composition "may act as a carrier for cortical, cancellous or cortical and cancellous bone chips. Such compositions are useful for filling larger bone voids. In addition, when these bone chips are not demineralized, they provide an added spectrum of biological properties not exhibited by the gelatin alone or the gelatin plus the osteogenic components (i-iv)."

Appellants argue

> Further, the specific language in the Wironen reference that discusses cancellous bone makes it clear that the reference only suggests the addition of such a component to the gelatin-based composition described therein. Specifically, the reference suggests that "[t]he composition according to this invention. . .may act as a carrier for cortical, cancellous, or cortical and cancellous bone chips." (page 13, lines 11-14 (emphasis added). The reference goes further to suggest that "such compositions are useful for fulfilling larger bone voids." (page 13, line 14 (emphasis added). Thus, it is clear that the Wironen reference only suggests the addition of cancellous bone to a gelatin based composition of the type described therein, meaning the composition exhibits the nonreversible gelation properties that are crucial to the invention described in Wironen.

Appellants' arguments are simply unpersuasive in view of the acknowledged benefits that the bone chips provide that are not exhibited by any of the other components of the composition of Wironen. These benefits include providing the volume for filling of larger bone voids and when not in demineralized form, providing an added spectrum of biological properties.

Finally, Appellants argue that the specific amounts are not suggested by the prior art. However, each of the prior art documents provide disclosure of suggested amounts that fall either within the range claimed by Appellants or sufficiently close to provide one

of ordinary skill at the time the invention was made to be able to engage permissible optimization. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

O'Leary teaches that the amount of demineralized bone powder can vary widely and is present in amounts from 5 to 80 weight percent. Appellants claim 10 – 100 parts (about 2 – 45 %). O'Leary states that the thickener (the component that is the same as Appellants' "plasticizer" is added in an amount sufficient to significantly improve the suspension-keeping characteristics of the composition. This amount is defined at about 2 to 10% (w/v) in Yim et al. and is claimed at 1 – 40 parts (about 0.2 – 23%). Yim et al. teach that the CSHS is present in amounts that provide the best handling properties both immediately after and 1 to 2 hours after preparation. One of ordinary skill in the art

with a reasonable amount of experimentation would clearly be able to determine the amounts required as claimed which require between about 80 - 120 parts (about 13 – 70%). The optimization of the amount of calcium sulfate and mixing solution to be further included is deemed well within the skill of the practitioner at the time the invention was made as it is clear that the amount of calcium sulfate is directly related to desired rate of set up of the composition, i.e. the more calcium sulfate used, the faster the composition will set up and harden. Further, it is clear that the amount of mixing solution is inversely related to the desired set up time and directly proportional to the ultimate consistency of the composition, i.e. the more mixing solution used, the more dilute the calcium sulfate and the slower the set up time but the more liquid the composition will become. Therefore, the Examiner has provided the evidence that optimization is well within the skill of the practitioner. With regard to the cancellous bone, the optimization of amounts is equally within the skill of the practitioner. Wironen discloses the purposes for the inclusion of the cancellous bone in bone implant compositions – to fill larger bone voids; therefore, optimization of amounts of cancellous bone to achieve these purposes are deemed also well within the skill of the practitioner. Further, the size of the cancellous bone chips is disclosed as being between 80 um –10 mm; the claims require particle sizes between 1 – 4 mm, well within the range disclosed by Wironen. The parts by weight are related to both the quantity and size of the bone chips to be used. It remains unclear as to how the practitioner would not be able to determine the size of the void to be filled and add as much cancellous bone as deemed necessary to fill the void. With regard to the production of the kit where the ingredients

are separated, it is clear that the components of the prior art are kept separate prior to formulation and subsequent use, particularly since the CSHS component must be kept anhydrous and therefore separate from the mixing solution since, upon combination with the mixing solution, the CSHS will become activated and begin to harden. Such activation is taught by the prior art references to be initiated immediately prior to implantation.

As evidenced by the discussion supra, the motivation to produce the claimed invention is clearly found in the cited prior art documents when their teachings are taken as a whole.

For the above reasons, it is believed that the rejections should be sustained.

(11) New Grounds of Rejection

APPROVED J.C.C. 6/27/05

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-8, 14-16, 20-21 of U.S. Patent No. 6,652,887 in view of WO 9840113 to Wironen.

Each of the elements of the patented claims is either the same as the elements of the instant claims or is a species of the generic elements of the instant claims. The instant claims also include a cancellous bone element. WO 9840113 is also drawn to a bone repair composition. The disclosed composition contains demineralized bone matrix, an inorganic component such as ceramics hydroxyapaptite and calcined bone, or bone morphogenic proteins or other growth factors and mixtures thereof. Other ingredients that may be present in the paste include wetting agents and carboxymethyl cellulose (see pages 5-6). At page 13, the reference states that the composition "may act as a carrier for cortical, cancellous or cortical and cancellous bone chips. Such compositions are useful for filling larger bone voids. In addition, when these bone chips are not demineralized, they provide an added spectrum of biological properties not exhibited by the gelatin alone or the gelatin plus the osteogenic components (i-iv)."

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include cancellous bone chips into the bone graft composition of U.S. Patent 6,652,887 for the benefit described in the disclosure of WO 9840113, i.e. they fill larger bone voids and provide an added spectrum of biological properties to the composition.

Claims 16-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 9-24 of copending Application No. 09/947,833. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-7 and 9-22 are a species of the generic claims drawn to the composition and therefore anticipate them.

With regard to kit claims 23 and 24, it would have been obvious to one of ordinary skill in the art to separate the mixing solution from the calcium sulfate hemihydrate due to the inherent property of calcium sulfate hemihydrate that causes it to harden upon hydration which would inherently render the composition useless.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-3, 8, 12-27, 29, and 32 of copending Application No. 09/327,761 in view of WO 9840113 to Wironen.

Each of the elements of the patented claims is either the same as the elements of the instant claims or is a species of the generic elements of the instant claims. The instant claims also include a cancellous bone element. WO 9840113 is also drawn to a bone repair composition. The disclosed composition contains demineralized bone matrix, an inorganic component such as ceramics hydroxyapaptite and calcined bone, or bone morphogenic proteins or other growth factors and mixtures thereof. Other ingredients that may be present in the paste include wetting agents and carboxymethyl cellulose (see pages 5-6). At page 13, the reference states that the composition "may act as a carrier for cortical, cancellous or cortical and cancellous bone chips. Such compositions are useful for filling larger bone voids. In addition, when these bone chips are not demineralized, they provide an added spectrum of biological properties not exhibited by the gelatin alone or the gelatin plus the osteogenic components (i-iv)."

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include cancellous bone chips into the bone graft composition of U.S. Patent 6,652,887 for the benefit described in the disclosure of WO 9840113, i.e. they fill larger bone voids and provide an added spectrum of biological properties to the composition.

This is a provisional obviousness-type double patenting rejection.

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